Impulse conduction in multiple sclerosis: a theoretical basis for modification by temperature and pharmacological agents

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SYNOPSIS The simplest model for explaining conduction defects in multiple sclerosis (MS) and other demyelinating diseases assumes that the only abnormality present is loss of myelin. The consequences of such an assumption have been investigated by numerical solution of a well-known set of differential equations describing conduction in a model demyelinated axon. In agreement with clinical findings, we show that this model predicts that the temperature at which conduction block occurs is a steep function of the extent of demyelination, so that small temperature increases may block large numbers of conducting fibres. Decreasing calcium concentration (or increasing pH) is calculated markedly to improve the conduction velocity of conducting demyelinated fibres and will, in addition, restore conduction in blocked fibres. The effects of other pharmacological agents have also been computed. The presence of a demyelinating lesion in a nerve fibre is shown greatly to impair the ability of the fibre to conduct repetitive impulses, conduction failing at much lower frequencies than in normal fibres. These calculations provide some insight into the nature of conduction defects in demyelinated nerve, demonstrate that many clinical features of MS are the expected consequences of loss of myelin and do not require the presence of other defects for their explanation, and provide a useful approach to the search for a symptomatic therapy.

Multiple sclerosis (MS) is a disease of the central nervous system in which the characteristic pathological alteration consists of myelin loss with a relative preservation of axis cylinders. It is generally believed that the clinical signs and symptoms in MS are the result of defects of impulse conduction in demyelinated axons of the central nervous system. A striking example of this is the central visual field defect associated with optic nerve lesions. Here there can be little doubt that the observed scotoma is related to a disturbance of conduction in a specific bundle of topographically oriented demyelinated fibres.

A spectrum of physiological abnormalities is seen in MS patients. In addition to apparent slowing and block of conduction (Namerow, 1968a), some fibres are unable faithfully to conduct repetitive impulses and appear to fatigue rapidly (Namerow, 1972). There is also a curious lability whereby clinical signs and symptoms can

fluctuate dramatically with small changes in the internal environment. Thus small changes in body temperature produce dramatic reversible alterations in the neurological signs and symptoms of MS, with heat causing a worsening (Nelson and McDowell, 1959; Namerow, 1968b) and cooling an improvement (Watson, 1959). Experimental evidence suggests that this phenomenon is caused by an effect of temperature on conduction in demyelinated axons (Davis, 1970; Davis and Jacobson, 1971; Rasminsky, 1972). Also, acute transient improvement in scotomas, nystagmus, and oculomotor paresis has been demonstrated in MS patients after procedures known to lower serum calcium concentration (Davis *et al.*, 1970).

The simplest possible model for MS (and presumably for other demyelinating diseases) assumes that the only defect present is loss of myelin without any concomitant pathological

alterations in the nerve membrane itself. Rasminsky and Sears (1972) have provided strong experimental evidence in rat ventral nerve root fibres demyelinated by injection of diphtheria toxin that the axon membrane in the internode is not excitable. Therefore, previous mathematical models demonstrated to describe conduction in myelinated nerve (Fitzhugh, 1962; Goldman and Albus, 1968) are modified to simulate myelin loss by only altering the myelin resistance and capacitance.

Smith and Koles (1970) and Koles and Rasminsky (1972) have investigated the effects of several morphological patterns of myelin loss (uniform demyelination of one or more internodes and paranodal demyelination) on conduction velocity using such a model system. In all cases they found conduction velocity to decrease with increasing demyelination until finally conduction block occurs, though the amount of myelin just sufficient to sustain conduction depends on the exact morphology.

We have extended calculations based on this model system to attempt to account for the complex clinical phenomena described earlier. These studies provide a unified account of temperature and calcium effects and suggest one possible cause of observed impairment in repetitive impulse conduction. In addition, they indicate a sound basis for the possible development of a symptomatic therapy for demyelinating diseases.

METHODS

The system of equations describing the model system is identical with that first presented by Goldman and Albus (1968) and modified to account for demyelination by Koles and Rasminsky (1972), except for changes in the voltage-dependent rate constants and permeability constants (equations 9–16 of Goldman and Albus, 1968) to account for the effects of changes in temperature, calcium concentration, and pH, and the application of pharmacological agents.

The model nerve consisted of 20 nodes with stimulating current applied to node 1 and with node 20 shorted to ground. The geometry was identical with that of Goldman and Albus (1968), with normal external myelin diameter chosen to be 30 μm . Paranodal demyelination is not a characteristic feature of MS, and hence, to account for demyelination, myelin resistance was usually uniformly decreased and myelin capacitance increased by an amount

appropriate for the degree of myelin loss (equations 2 and 3 of Goldman and Albus, 1968) and expressed as a fraction of the normal resistance. We assumed demyelination to begin at node 4 and proceed to the end of the fibre, except in those cases where a single demyelinated internode was studied. All constants and initial conditions are given in Goldman and Albus (1968, Appendix). Note that the experimental data from which these equations were derived were obtained at 20°C, which is consequently the reference temperature for our calculations.

The value of 30 μm chosen for normal external myelin diameter is at the upper range of real fibre diameters. This was used in order to have values for conduction velocities which were large, so as to minimize running time for the computer programmes. The work of Goldman and Albus (1968) shows that as long as the relationships between *normal* external myelin diameter, axis cylinder diameter, and internodal distance remain constant, the only effect of changing fibre diameter is to scale the conduction velocity by a constant factor proportional to diameter.

TABLE
EXPERIMENTAL EFFECTS OF ALTERATIONS IN TEMPERATURE
AND CALCIUM CONCENTRATION

Parameter	Q_{10}^*	mV shift per† e-fold change in $[Ca^{++}]$
$\bar{P}_{Na}$	1.3	—
P'_K	1.2	—
$\bar{P}_P$	1.2	—
α_m	1.8	8.6
β_m	1.7	8.6
α_h	2.8	7.4
β_h	2.9	7.4
α_n	3.2	0.8
β_n	2.8	0.8
α_p	3.0‡	0.0‡
β_p	3.0‡	0.0‡

* Data from Frankenhaeuser (1963).

† Data from Hille (1968). Note that Hille presented his results as shifts in time constants and steady-state levels for the various parameters, not directly as rate constants. The values here are derived from his data.

‡ Values assumed. Experimental data not available.

The effects of temperature variation were allowed for by scaling all rate constants and permeability constants by the experimentally determined Q_{10} 's (Frankenhaeuser and Moore, 1963; Frankenhaeuser, 1965) (Table). This method of incorporating the effect of temperature is justified by the experimental

data and has been shown to produce in model nerve fibres calculated responses which are in agreement with observations on normal living nerve (Hodgkin and Huxley, 1952; Huxley, 1959; Frankenhaeuser, 1965; Cooley and Dodge, 1966; Smith and Koles, 1970). The effect of temperature on the myelin resistance and capacitance and axoplasmic resistivity is not likely to be a significant factor, but in any case could not be taken into account for lack of adequate experimental data.

The effects of calcium and pH were calculated by translating the functions describing the voltage-dependent rate constants along the voltage axis according to experimental data (Hille, 1968—see Table). This general procedure has also been justified by computations of the effect of calcium on conduction in normal, unmyelinated nerve (Huxley, 1959).

The differential equations were converted to difference form and integrated using a fourth-order Runge-Kutta procedure on IBM 370/155 and SPC

16/65 digital computers. In most cases the fibre was sampled at each node and at space increments of 1/10 the internodal distance. Time increments were automatically adjusted to maintain errors in voltage at less than $10 \mu\text{V}$.

NUMERICAL COMPUTATIONS

EFFECTS OF TEMPERATURE Figures 1 and 2 show the results of the computations we have carried out to examine the combined effects of temperature and loss of myelin on conduction. Figure 1 gives the calculated conduction velocity as a function of temperature for a normal nerve fibre (top curve) and a series of fibres subjected to increasing amounts of demyelination (0.5, 0.33, 0.2, 0.1, and 0.06 times the normal myelin resistance). In each curve the last point at the right is at the highest temperature at which conduction occurs. A temperature 3°C higher does not permit conduction, as indicated by the dashed lines.

The conduction velocity of normal nerve increases with increasing temperature over a broad range, reaches a maximum at about 42°C , and then decreases before block. This result, includ-

FIG. 1. Calculated values of conduction velocity as a function of temperature for a normal nerve fibre (upper curve) and fibres with increasing loss of myelin. For each curve the last datum point at the right is for the highest temperature at which continuous conduction is possible, the dashed lines and arrows simply being a convenient means of indicating block of conduction at a temperature 3°C greater. The amount of demyelination is expressed in terms of the myelin resistance relative to normal.

FIG. 2. Blocking temperature as a function of the amount of myelin loss. The error bars correspond to an uncertainty of 2°C . The amount of demyelination is expressed in terms of the myelin resistance relative to normal.

ing the calculated presence of a maximum, is similar to that calculated for the squid giant axon (Huxley, 1959). In demyelinated fibres the conduction velocity also generally increases with increasing temperature, although the slope is reduced. In addition, the presence of a maximum and the subsequent decrease become less apparent with increasing loss of myelin.

As myelin is lost, conduction fails at progressively lower temperatures. Particularly with substantial amounts of demyelination, the blocking temperature is a steep function of the amount of myelin present (Fig. 2). To put the result another way, given a population of fibres with varying amounts of myelin lost (such as would be expected to occur in a real lesion), a small increase in temperature would substantially decrease the number of fibres whose blocking temperature exceeds the body temperature and thus will reduce the number of conducting fibres. At the same time that more fibres are blocked, the conduction velocity of those fibres which remain conducting will generally tend to be increased.

Since a demyelinated axon is seen to be in a delicate balance between conducting and blocked states, any factor serving to depress function slightly would have dramatic effects on demyelinated nerve, although possibly having little noticeable effect on normal fibres. Thus, decreasing the maximum sodium permeability by 20% decreases the action potential in normal nerve by only 3 mV, yet we calculate it to cause a further 5° C lowering of the blocking temperature of a 90% demyelinated fibre.

Decreases in axis cylinder diameter (Greenfield, 1958), due possibly to oedema, can occur in multiple sclerosis. The lower curve in Fig. 6 shows the effect of a 50% decrease in diameter occurring in a demyelinated region of nerve. The blocking temperature is decreased (middle curve) by an additional 15° C for any particular amount of demyelination. Obviously, a substantial degree of additional clinical dysfunction would be expected to result from such a situation.

EFFECTS OF CALCIUM AND pH Figure 3a illustrates the effect of an e-fold (approximately 63%) decrease in calcium concentration on conduction in fibres with 10% and 20% normal myelin. The solid curves are reproduced from Fig. 1 for

FIG. 3a. Conduction velocity as a function of temperature calculated for fibres with 10% normal myelin resistance ($\circ$, $\bullet$) and 20% normal ($\triangle$, $\blacktriangle$) in normal Ringer's solution ($\bullet$, $\blacktriangle$ —from Fig. 3) and Ringer's solution with $1/e^{\text{th}}$ normal calcium ($\circ$, $\triangle$). As in Fig. 3, the datum point at the highest temperature in each curve represents the maximum temperature at which continuous conduction is possible.

convenience. As in Fig. 1, the last point on the right is at the highest temperature capable of sustaining conduction. In both cases, at temperatures lower than the blocking temperature, a decrease in calcium concentration increases conduction velocity by 40–50%. In addition to this, reductions in calcium concentration cause the

FIG. 3b. Blocking temperature (error bars) and conduction velocity ($\bullet$) as a function of the calcium concentration for a fibre with 10% normal myelin resistance. Note that the abscissa is logarithmic.

blocking temperature to increase toward normal, and this effect is most predominant in severely demyelinated fibres.

Figure 3b shows that both the blocking temperature and the conduction velocity are linear functions of the logarithm of the calcium concentration. This figure is for a fibre with 10% normal myelination. If a larger amount of myelin is present, the slope of the curve relating blocking temperature to calcium concentration is decreased.

Thus, the result of decreasing the calcium concentration in a population of fibres having different amounts of myelin lost is predicted to be an increase in the number of conducting fibres, combined with a restoration of the conduction velocity toward more normal values in those fibres which were not blocked at normal calcium levels. This is in contrast with the effects of temperature in which cooling increases the number of conducting fibres but decreases conduction velocity in those which were not blocked.

Increasing pH acts on the rate constants in the same direction as decreases in calcium concentration. Detailed calculations were not performed, but since the rate constants shift by only 1.3 mV per e-fold change in hydrogen ion concentration (3.0 mV per pH unit) at physiological pH (Hille, 1968), we may conclude that this alteration would be much less effective than similar changes in calcium concentration.

Effects qualitatively similar to these have also been calculated for the other morphological patterns of myelin loss considered by Koles and Rasminsky (1972). Reducing calcium concentra-

tion will restore conduction in a fibre blocked by demyelination of a single internode or by paranodal demyelination.

RESPONSES TO REPETITIVE STIMULATION The response of the model axon to a second stimulus delivered at a variable time after an initial stimulus is shown in Fig. 4 for both a normal nerve and a nerve which has lost all but 10% of its myelin. The action potential amplitude and conduction velocity resulting from the initial stimulus were 110.4 mV and 37.8 m/sec for normal nerve, and 90.0 mV and 8.7 m/sec for the 90% demyelinated fibre. To prepare Fig. 4, the magnitude and conduction velocity of the response produced by a second impulse were divided by the corresponding values for the initial response for both normal and demyelinated nerve.

For normal nerve, a second stimulus at 1.85 msec after the initial stimulus is unable to produce a response, whereas at 2.04 msec a second response with initial amplitude and conduction velocity of 69 mV and 14.6 m/sec is produced. Intermediate times were not explored. With increasing time between the stimuli the amplitude and velocity of the second response increase rapidly toward initial values. During the interval in which a second response is reduced, the second response is continually lagging behind the initial impulse, while gradually recovering its amplitude and velocity. Whether substantial changes in frequency occur depends on the conduction distance involved.

In the case of a 90% demyelinated fibre, a

FIG. 4. Calculated responses of a normal nerve and a nerve with 10% normal myelin resistance to pairs of stimuli. The abscissa is the time between stimuli. The ordinate plots the ratio $\frac{\text{action potential amplitude elicited by second stimulus}}{\text{action potential amplitude elicited by initial stimulus}}$ and a similar ratio for the conduction velocities. The temperature is 20° C. At intervals less than 1.85 msec (normal nerve) and 4.7 msec (demyelinated nerve) a second response cannot be elicited. These points are indicated on the abscissa.

FIG. 5. Conduction velocity as a function of temperature calculated for fibres with 10% normal myelin resistance ($\circ$, $\bullet$) and 20% normal ($\triangle$, $\blacktriangle$) for the situation in which the inactivation time constant is normal ($\bullet$, $\blacktriangle$ —from Fig. 3) and the case where the inactivation time constant is increased by a factor of 4 ($\circ$, $\triangle$).

second stimulus at 4.7 msec fails to produce a response, and at 5.0 msec a response with initial amplitude of 70 mV and velocity of 4.7 m/sec results. Again, intermediate times were not examined. With an interval of more than 5.0 msec, the initial amplitude and velocity again recover.

Therefore, if we consider a pair of impulses 4.7 msec apart travelling in a fibre which contains a zone which is 90% demyelinated, only the first impulse will pass through. With larger amounts of myelin loss, the situation rapidly becomes worse.

This increase in refractory period of transmission (RPT) from 1.95 ± 0.1 msec in normal nerve to 4.85 ± 0.15 msec in 90% demyelinated nerve is much larger than that which would be expected simply from a consideration of the time course of the permeability variables during the action potential. In 90% demyelinated nerve at 4.0 msec after the start of the initial response, the values of the permeability variables have recovered to values which are as close or closer to their resting states than those at 3.2 msec in

normal nerve, where conduction is nearly normal. The fibre remains blocked because of the much greater shunting of current in the demyelinated internode.

Such increases in refractory period of transmission are most noticeable in fibres demyelinated nearly to the point of conduction block. Thus, a fibre with 20% normal myelin resistance is calculated to have an RPT of 2.65 ± 0.1 msec, which is an increase of only 35% relative to normal, compared with the 250% increase seen in the case of 90% demyelination. A fibre with 50% normal myelin resistance shows an almost normal RPT of 2.1 ± 0.1 msec.

Decreases in calcium concentration are calculated to improve substantially the ability of demyelinated nerve to transmit repetitive impulses. Thus, for 90% demyelinated nerve, an e-fold decrease in calcium concentration results in a decrease in the refractory period of transmission from 4.85 ± 0.15 msec to 3.6 ± 0.1 msec. Larger effects of calcium are observed in fibres which are more severely demyelinated.

FIG. 6. Blocking temperature as a function of the relative myelin resistance for the situation in which the inactivation time constant has been increased by a factor of 4 (—) and for the case where in addition to loss of myelin there is a twofold decrease in axis cylinder diameter (— · —). The curve of Fig. 2 for myelin loss alone is reproduced for convenience.

PHARMACOLOGICAL EFFECTS This model system provides a convenient means of defining the manner in which the kinetic properties of the nerve membrane should be altered in order to improve conduction in demyelinated nerve. Presumably such effects occurring in MS patients would improve clinical signs and symptoms. We have already described the effects of temperature, calcium, and pH. Conduction in demyelinated nerve is improved by factors which increase the duration of the action potential without adversely affecting conduction velocity or action potential amplitude, since the total membrane current is increased. This may be accomplished by reducing the contribution of the steady-state conductance, or prolonging the sodium conductance by slowing the inactivation process.

Figures 5 and 6 illustrate the effect of a four-fold increase in the sodium inactivation time constant, τ_h . This alteration results in an action potential in normal nerve which is about 2.5 times as long. Figure 5 shows that when applied to a demyelinated fibre, this procedure does not appreciably affect the conduction velocity but greatly increases the blocking temperature for any amount of demyelination. This is more clearly seen in the upper curve of Fig. 6. The curve relating blocking temperature and amount of myelin is shifted vertically by more than 15° C. Thus at any given temperature conduction is possible with far less myelin.

Reduction of the maximum potassium permeability will also improve conduction in demyelinated nerve by increasing the blocking temperature, but the effects are not as dramatic. Thus, a 50% decrease in P'_k increases the blocking temperature of an 80% demyelinated fibre by only 2° C. This is due to the fact that the increasing potassium permeability does not contribute as much to the falling phase of the action potential as the simultaneous inactivation of the sodium permeability. A 50% decrease in maximum potassium permeability prolongs the normal action potential only by about 10% and does not affect conduction velocity at all.

DISCUSSION

It should be stressed that the procedure of using a mathematical model to study the behaviour of a demyelinated axon has a great deal of experi-

mental justification. Fitzhugh (1962) first described the procedure for combining the phenomenological description of the behaviour of excitable membranes contained in the Hodgkin-Huxley equations (Hodgkin and Huxley, 1952) with the equations for a passive cable (Hodgkin and Rushton, 1946) to yield a description of conducted action potentials in myelinated nerve. Goldman and Albus (1968) extended this work by replacing the Hodgkin-Huxley equations, which describe the behaviour of the squid giant axon, with a similar set of relationships (the Frankenhaeuser-Huxley equations) which were developed by the application of the voltage clamp technique to the myelinated nerve fibre (Dodge and Frankenhaeuser, 1958, 1959; Frankenhaeuser, 1959, 1960, 1962a-c, 1963a, b; Frankenhaeuser and Huxley, 1964).

The calculations of these and other investigators concerning the behaviour of normal myelinated fibres (Frankenhaeuser and Huxley, 1964; Frankenhaeuser, 1965; Hutchinson *et al.*, 1970), combined with similar computations of membrane action potentials (Huxley, 1959; Fitzhugh, 1960; Fishman, 1970) and propagated activity (Cooley and Dodge, 1966) in non-myelinated fibres, have provided compelling evidence for accepting these models as excellent descriptions of living nerve fibres under a variety of environmental conditions.

The calculations of Smith and Koles (1970) and Koles and Rasminsky (1972), when compared with the experimental data of Rasminsky and Sears (1972), demonstrate the ability of this model to simulate accurately the behaviour of real demyelinated fibres.

Koles and Rasminsky (1972) briefly reported one calculation concerning the increased velocity and subsequent block produced by warming a paranodally demyelinated fibre barely conducting at 20° C, and mentioned that this qualitatively agreed with experimental observations of Rasminsky (1971) on rat ventral root fibres demyelinated by diphtheria toxin. The complete family of curves shown in Fig. 1 contains quite complex behaviour, and it would be an excellent test of the model's accuracy to see if there is agreement with experimental observations over the entire range.

The calculated relationships of Figs 1 and 2, in addition to indicating that increased numbers

of demyelinated fibres are blocked with temperature elevation, suggest that the clinical worsening with hyperthermia seen in MS patients (Nelson and McDowell, 1959; Watson, 1959; Namerow, 1968b) is caused by block of conduction alone, and not by any change in conduction velocity. Since the low conduction velocity in demyelinated nerve increases with increased temperature, this factor would, if anything, be expected to improve clinical function.

We may also offer an explanation for the observation that increasing temperature enlarges the size of a central scotoma. There exists compelling evidence that a plaque enlarges by peripheral extension (Lumsden, 1970), with the severest or completely demyelinated fibres generally at the centre, and lesser degrees of involvement toward the periphery. Since totally demyelinated internodes are already blocked (Fig. 1), the blocking effect of hyperthermia is most likely to be on the partially demyelinated axons distributed in greater numbers more peripherally.

This model provides a reasonable explanation for the effects of hypocalcaemia observed clinically. In addition to the acute improvement in scotomas, nystagmus, and oculomotor paresis with intravenous NaHCO_3 or edetate (EDTA) referred to earlier, a more recent study indicates that large doses of oral phosphate cause improvement in visual function measured by acuity, field, and pupillometry tests (Becker *et al.*, 1973). Hypocalcaemia is calculated to restore conduction in blocked demyelinated fibres and to increase substantially the conduction velocity of conducting fibres. Both changes would tend to restore function. Note that NaHCO_3 serves to increase pH in addition to decreasing calcium concentration, and that both alterations are calculated to be beneficial.

In segmentally demyelinated peripheral nerves, conduction failure has been observed at lower frequencies than in normal nerve (Cragg and Thomas, 1964; Davis, 1972). Patients with MS have been observed to exhibit defects in the cortical evoked response after peripheral nerve stimulation at frequencies below 100 Hz (Namerow, 1972). McDonald and Sears (1970) studied lesions induced in the dorsolateral sulcus of the cat spinal cord by injection of diphtheria toxin and found the refractory period for *in situ*

stimulation to be increased by up to fourfold in fibres traversing the demyelinating lesion. The prediction of this model that the absolute refractory period is increased to approximately 2.5 times normal in a 90% demyelinated fibre seems in reasonable accord with these observations. The implications of such defects for information processing in the central nervous system are enormous, the presence of a demyelinating lesion causing the fibre to act as a filtering device.

The effects of decreased potassium permeability and increased inactivation time constant were studied because there exist pharmacological agents having primarily these effects. Thus, tetraethylammonium (TEA) chloride will block the potassium permeability of myelinated nerve quite specifically (Hille, 1967). Both DDT and scorpion venom slow the sodium inactivation process, although both are irreversible, tend to be progressive in their effect, and are not completely specific for sodium inactivation (Narahashi and Haas, 1968, 1972). Condylactis toxin very specifically slows sodium inactivation but shares the disadvantage of being irreversible and progressive (Narahashi *et al.*, 1969).

Though these particular agents have not been tested in model demyelinated nerve, the computations do serve to indicate the direction a pharmacological approach should take in terms of the underlying kinetic processes. Agents which serve to decrease the contribution of the potassium permeability are not likely to be very satisfactory in restoring conduction to demyelinated fibres because the time course of the action potential in this model system is much less sensitive to changes in potassium activation than sodium inactivation. For clinical purposes, it is suggested that it might be fruitful to try to develop an agent having a specific, reversible, and easily controlled effect on the sodium inactivation process.

We have attempted to extend a well-known theoretical model of impulse conduction in demyelinated nerve in order to understand better a variety of physiological abnormalities and to point out related clinical implications. In the present instance, the model says in a rather striking way that many of the pathophysiological and clinical features of MS are accounted for on the assumption that myelin loss is the only defect

present. Also, the theoretical effects of a variety of pharmacological agents on conduction in demyelinated nerve can be predicted given a sufficiently detailed understanding of their effects on normal nerve fibres. Whether this approach will lead to any clinically useful therapeutic agent is unknown, but the basic idea seems scientifically sound and worthy of further investigation.

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